REMARKS

The Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Amendments to the Claims

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 63, 67, 68, and 75-77 are currently being amended to further prosecution.

Claim 63 has been amended to omit recitation of "fragment of SEQ ID NO:2." Furthermore, claim 63 has been amended to recite the phrase "comprising a mutation selected from the group consisting of" rather than the phrase "that includes." Support for the amendments to claim 63 is provided in the original claims and specification as filed. For example, support for amended claim 63 is provided in the specification at page 5, lines 7-13 (reciting a definition for "variant").

Claims 63, 67, 68, and 75-77 are amended to recite "or other antigen-specific binding molecule." Support for this amendment is provided in the original claims and specification as filed. For example, the specification states that:

> Antibodies specific for ADEC may be produced by inoculation of an appropriate animal with the polypeptide or ***an antigenic fragment***. An antibody is specific for ADEC if it is produced against an epitope of the polypeptide and binds to at least part of the natural or recombinant protein. Induction of antibodies includes not only the stimulation of an immune response by injection into animals, but also analogous steps in the production of ***synthetic antibodies or other specific-binding molecules*** such as the screening of recombinant immunoglobulin libraries (cf. Orlandi R et al (1989) Proc Natl Acad Sci USA 86:3833-3837, or Huse W D et al (1989) Science 256:1275-1281) or the in vitro stimulation of lymphocyte populations. Current technology (Winter G and Milstein C (1991) Nature 349:293-299) provides for a number of ***highly specific binding reagents based on the principles of antibody formation***. These techniques may be adapted to produce molecules specifically binding ADEC.

(*See* specification at page 10, lines 25-36 (emphasis added)).

Claim 77 has been amended to recite "under stringent conditions comprising washing at 68°C in a solution of 0.2 × SSC and 0.1% SDS." Support for this amendment is provided, for example, in the specification at page 6, lines 4-19 and at page 7, line 23 to page 8, line 2. In particular, at page 7, line 23 to page 8, line 2, the specification states:

> Although nucleotide sequences which encode ADEC and/or ADEC variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring ADEC gene under ***stringent conditions***, it may be advantageous to produce nucleotide sequences encoding ADEC or ADEC derivatives possessing a substantially different codon usage....
>
> Nucleotide sequences encoding ADEC may be joined to a variety of other nucleotide sequences by means of well established recombinant DNA techniques (cf. ***Sambrook J et al.*** (1989) Molecular Cloning: A Laboratory Manual, 2nd Ed, Cold Spring Harbor, N.Y.

As indicated in the specification, the Sambrook *et al.* laboratory manual provides "well established recombinant DNA techniques." Furthermore, the Sambrook *et al.* laboratory manual is incorporated by reference in the present specification at page 6, line 19. At page 6, lines 4-19, the specification states:

> "Oligonucleotides" or "nucleic acid probes" are prepared based on the cDNA sequence which encodes ADEC provided by the present invention....[T]hese probes may be used to determine whether mRNA encoding ADEC is present in a cell or tissue or ***to isolate similar nucleic acid sequences from chromosomal DNA*** as described by Walsh P S et al (1992) PCR Methods AppI 1:241-250.
>
> Probes may be derived from naturally occurring or recombinant single- or double-stranded nucleic acids or be chemically synthesized....Probes of the present invention, their preparation and/or labeling are elaborated in ***Sambrook J et al*** (1989) Molecular Cloning: A Laboratory Manual, 2nd Ed, Cold Spring Harbor, N.Y.; or Ausubel F M et al (1989) Current Protocols in Molecular Biology, Vol 2, John Wiley & Sons, ***both incorporated herein by reference.***

In particular, the Sambrook *et al.* laboratory manual states that "if the experiment demands washing at ***high stringencies***, immerse the filters for 60 minutes in 300-500 ml of a solution of ***0.2 × SSC and 0.1% SDS at 68°C.***" *See* Sambrook *et al.*, section 1.103, n. 7 (emphasis added) (copy provided herewith). Accordingly, claim 77 has been amended to recite these well established stringent washing conditions.

After amending the claims as set forth above, claims 63-77 are now pending in this application. Claims 70 and 71 currently are withdrawn from consideration in view of the Examiner's restriction requirement.

II. Rejection - 35 U.S.C. § 112, first paragraph, "written description"

Claims 63-69 and 72-77 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Applicants respectfully traverse the rejection in view of the foregoing amendments and for the following reasons.

Claim 63 has been amended to omit recitation of "fragment of SEQ ID NO:2." Furthermore, claim 63 has been amended to recite a selected group of variants. These include: (i) a conservative amino acid substitution in SEQ ID NO:2; (ii) an insertion of from 1-5 amino acids in SEQ ID NO:2; and (iii) a deletion of from 1-5 amino acids in SEQ ID NO:2. Furthermore, claim 63 recites that the polypeptide has chemotactic activity or activates neutrophils or monocytes.

Claim 77 has been amended to recite specific "stringent conditions" for hybridization. Furthermore, claim 77 recites that the encoded polypeptide "has chemotactic activity or activates neutrophils or monocytes."

The U.S. PTO has provided a "Synopsis of Application of Written Description Guidelines" [hereinafter "Guidelines"] (copy provided herewith). Example 13 of the Guidelines provides a claim related to a "protein variant." In Example 13, adequate support for a claim to a "protein variant" is not found where

> The specification and claim do not indicate what distinguishing attributes [are] shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO:[X].

See Guidelines, page 50, Example 13.

In contrast, claim 63 does recite "distinguishing attributes shared by the members of the genus." For example, claim 63 recites that "the polypeptide has chemotactic activity or activates neutrophils or monocytes." Furthermore, claim 63 places a limit on the "number of amino acid substitutions, deletions, insertions and/or additions" that may be made to SEQ ID NO:2. Claim 63 recites the phrase "selected from the group consisting of: (i) a conservative amino acid substitution in SEQ ID NO:2; (ii) an insertion of from 1-5 amino acids in SEQ ID NO:2; and (iii) a deletion of from 1-5 amino acids in SEQ ID NO:2."

Example 14 of the Guidelines provides a claim related to a "product-by-function." *See* Guidelines, page 53. In Example 14, adequate support for a claim to a "protein variant" is found where the claim recites "variants thereof that are at least 95% identical to SEQ ID NO:[X] and catalyze the reaction A→B." In comparison, claim 63 recites: (i) a conservative amino acid substitution in SEQ ID NO:2; (ii) an insertion of from 1-5 amino acids in SEQ ID NO:2; and (iii) a deletion of from 1-5 amino acids in SEQ ID NO:2. Because SEQ ID NO:2 includes 109 amino acids, the "substitution," "insertion," or "deletion" recited in claim 63 would result in a polypeptide that has greater than 95% sequence identity to SEQ ID NO:2. For example, a variant having a 5 amino acid deletion would have 104/109 amino acid identity to the polypeptide of SEQ ID NO:2 (or 95.4% sequence identity). Furthermore, as noted above, claim 63 recites that the polypeptide has a "function" where claim 63 recites that "the polypeptide has chemotactic activity or activates neutrophils or monocytes."

With respect to claim 77, Example 9 of the Guidelines provides a claim related to "hybridization." *See* Guidelines, page 34. In Example 9, adequate support is found where a claim recites "highly stringent hybridization conditions...in combination with the coding function of DNA." In comparison, claim 77 recites what would be considered to be "highly stringent hybridization conditions" as indicated in the Sambrook *et al.* laboratory manual. Claim 77 also provides a "coding function" for the recited polynucleotide where claim 77 recites that the encoded polypeptide "has chemotactic activity or activates neutrophils or monocytes."

As such, the Applicants have amended the claims based on the Written Description Guidelines provided by the U.S. PTO. For these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, for inadequate written description are requested.

III. Rejection - 35 U.S.C. § 112, first paragraph, "enablement"

Claims 63-69 and 72-77 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly "because the specification, while being enabling for an isolated antibody which specifically binds a protein consisting of the amino acid sequence set forth in SEQ ID NO:2 does not reasonably provide enablement for an isolated antibody to a polypeptide variant of SEQ ID NO:2 as recited in claim 63 or a polypeptide variant as recited in claim 77(b)." The Applicants respectfully traverse the rejection in view of the foregoing amendments and for the following reasons.

As indicated above, claim 63 has been amended to omit recitation of "fragment of SEQ ID NO:2." Furthermore, claim 63 has been amended to recite a selected group of variants. These include: (i) a conservative amino acid substitution in SEQ ID NO:2; (ii) an insertion of from 1-5 amino acids in SEQ ID NO:2; and (iii) a deletion of from 1-5 amino acids in SEQ ID NO:2. In addition, claim 63 recites that the polypeptide has chemotactic activity or activates neutrophils or monocytes.

Claim 77 has been amended to recite specific "stringent conditions" for hybridization. Furthermore, claim 77 recites that the encoded polypeptide has chemotactic activity or activates neutrophils or monocytes.

One skilled in the art would not have to undertake "undue experimentation" to make and use the subject matter as recited in the amended claims. First, SEQ ID NO:2 is a relatively small polypeptide having only 109 amino acids. Therefore, the possible number of variants is limited.

Furthermore, the claims recite that the polypeptide has "chemotactic activity" or "activate neutrophils or monocytes." The specification provides methods for "Determination of ADEC-Induced Chemotaxis or Cell Activation" (see page 18, line 29 to page 19, line 29) which methods further are known in the art. Therefore, one of skill in the art has a method for testing the recited subject matter.

In addition, the specification provides guidance as to what portions of SEQ ID NO:2 may be necessary or sufficient for activity. For example, the specification provides an alignment of SEQ ID NO:2 with other human chemokines of the C-X-C family at Figure 2. This provides guidance as to which amino acids of SEQ ID NO:2 are conserved among human C-X-C chemokines and may be necessary or sufficient for activity. For example, all of the chemokines in Figure 2 have a leucine-rich region (see, e.g., aa 8-13 of SEQ ID NO:2). All of the cytokines in Figure 2 include a C-X-C motif (see, e.g., aa 33-35 of SEQ ID NO:2). These conserved regions as well as many other conserved amino acids serve as "guideposts" for identifying portions that are necessary or sufficient for biological activity.

In addition to the alignment at Figure 2, the specification provides a hydrophilicity plot and an antigenic index plot at Figure 4. This provides even further guidance as to which portions of SEQ ID NO:2 may be necessary and sufficient for biological activity by indicating which portions of SEQ ID NO:2 are likely to be on the surface of the polypeptide.

Based on this information, one of skill in the art could obtain variants as recited in the claims without having to undertake undue experimentation. For example, one skilled in the art could synthesize chimeric variants of SEQ ID NO:2 and the other human chemokines of the C-X-C family, exchanging conserved or non-conserved regions, to identify portions of SEQ ID NO:2 that are necessary or sufficient for activity. None of these methods would require undue experimentation because one of skill in the art has been provided with all the necessary tools and information for performing the methods. Furthermore, the Applicants have provided "guideposts" that one of skill in the art could use when designing variants.

For these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement are requested.

IV. Rejection - 35 U.S.C. § 112, second paragraph

Claims 63-69 and 72-77 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Applicants respectfully traverse the rejection in view of the foregoing amendments and for the following reasons.

Claim 63 was rejected for reciting the terms "including" and "includes." As amended, claim 63 does not recite the terms "including" or "includes."

Claims 63, 67-68, and 75-77 were rejected in the final Office Action dated April 26, 2006, as allegedly "vague and indefinite" under 35 U.S.C. § 112, second paragraph, for reciting "specific binding molecule." In response, the Applicants proposed to amend the claims to recite "antigen-specific binding molecule." However, the Advisory Action dated August 4, 2006 asserts that the limitation "antigen-specific binding molecule" is unclear "because it encompasses for example 'antagonist' molecules to the polypeptide of SEQ ID NO:2, but the specification fails to provide a proper definition or written description for such molecules." (*See* Advisory Action at page 3). The Applicants respectfully disagree.

One skilled in the art would recognize that an "antigen-specific binding molecule" includes an antigen-specific portion of an antibody. Furthermore, the specification provides a written description for an "antigen-specific binding molecule." The specification states that "[a]ntibodies specific for ADEC may be produced by inoculation of an appropriate animal with the polypeptide or an antigenic fragment." (*See* page 10, lines 25-26). As such, an antibody would be viewed as an "antigen-specific binding molecule." Furthermore, the specification states that "[i]nduction of antibodies includes not only the stimulation of an immune response by injection into animals, but also analogous steps in the production of ***synthetic antibodies or other specific-binding molecules*** such as the screening of recombinant immunoglobulin libraries." (*See* page 10, lines 28-33; citing Orlandi *et al.*, PNAS (1989) 86:3833-3837 [hereinafter "Orlandi *et al.*"] (copy provided herewith) and Huse *et al.*, SCIENCE (1989) 256:1275-1281 [hereinafter Huse *et al.*] (copy provided herewith)). Orlandi *et al.* and Huse *et al.* disclose the production of recombinant "antigen-specific binding molecules" such as Fv or Fab fragments. The specification also states that current technology "provides for a number of highly specific binding reagents ***based on the principles of antibody formation*** [and that these] techniques may be adapted to produce molecules specifically binding ADEC." (*See* page 10, lines 33-36 (emphasis added); citing Winter *et al.*, NATURE (1991) 349:293-299 [hereinafter Winter *et al.*] (copy provided

herewith)). Winter *et al.* also disclose the production of recombinant "antigen-specific binding molecules."

Therefore, the metes and bounds of the term "antigen-specific binding molecule" would be understood by those skilled in the art and furthermore, the specification provides a written description of an "antigen-specific binding molecule."

Claim 77 was rejected for reciting the phrase "hybridizes under stringent conditions." The Examiner indicated that the "rejection could be obviated by supplying specific conditions supported by the specification which Applicants consider to be 'stringent.'" As indicated above, the Applicants have amended claim 77 to recite specific hybridization conditions as provided in the Sambrook *et al.* laboratory manual, which is incorporated in the present specification by reference.

For these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are requested.

V. Rejection - 35 U.S.C. § 102

Claims 63-67, 76 and 77 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Li *et al.* (U.S. Pat. No. 6,174,995) [hereinafter "Li"]. The Applicants respectfully traverse the rejection in view of the foregoing amendments and for the following reasons.

Li does not teach or suggest a polypeptide or polynucleotide as recited in the rejected claims. A BLAST alignment of SEQ ID NO:2 and MCP-4 indicates that the two polypeptides have 33% sequence identity within a portion of SEQ ID NO:2 from amino acids 60-95 and within a portion of MCP-4 from amino acids 53-93 (copy provided herewith). Other than between these portions of SEQ ID NO:2 and MCP-4, the BLAST alignment finds no further similarity. Therefore, Li does not disclose a polypeptide of SEQ ID NO:2 or a variant as recited in claim 63.

A BLAST alignment of SEQ ID NO:1 and the gene for MCP-4 indicates that the two polynucleotides have "no significant similarity" (copy provided herewith). As would be understood by one skilled in the art, a polynucleotide having "no significant similarity" to another polynucleotide will not hybridize to the complement of the other polynucleotide under stringent conditions. Therefore, Li does not disclose a polynucleotide of SEQ ID NO:1 or a polynucleotide that will hybridize to the complement polynucleotide sequence of SEQ ID NO:1 under stringent conditions as recited in claim 77.

Because Li does not teach or suggest a polypeptide or polynucleotide as recited in the rejected claims, Li does not anticipate the claimed subject matter. For these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) are requested.

VI. Rejection - 35 U.S.C. § 103

Claims 63, 68 and 69 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Li as applied to claims 63-67, 76 and 77 above, and further in view of Hart (U.S. Pat. No. 5,094,941) [hereinafter "Hart"]. The Applicants respectfully traverse the rejection in view of the foregoing amendments and for the following reasons.

As indicated above, Li does not teach or suggest a polypeptide or polynucleotide as recited in the rejected claims. Because Li does not teach or suggest a polypeptide or polynucleotide as recited in the rejected claims, Li does not render the claimed subject matter obvious.

For these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are requested.

VII. Claim Rejections – Double Patenting

Claims 63-69 and 72-77 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,692,920 ("the '920 Patent"). The Applicants have submitted herewith a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321 to overcome the rejection.

Reconsideration and withdrawal of the rejection under the judicially created doctrine of obviousness-type double patenting are requested.

VIII. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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